

## Supporting Information – Sex differences in parent-offspring recurrence of attention-deficit/hyperactivity disorder – by Solberg *et al.*

### Appendix S1. Description of the registries.

The nationwide Medical Birth Registry of Norway (MBRN) was established in 1967 and contains information about all births in Norway, including spontaneous abortions and stillbirths from 16 weeks of gestation (1). The aim of the registry is to clarify causes and consequences of health problems related to pregnancy and birth, and monitor the incidence of adverse outcomes. The registry is based on compulsory notification and includes data on maternal health before and during pregnancy, labour complications and interventions, and birth outcomes. Information on the father is also included in the registry.

The Norwegian Prescription Database (NorPD) contains data about all dispensed drugs in Norway since 2004. The aim of the NorPD is to collect and process data on drug consumption. Drugs that are purchased without prescription are not included, and medication given to an individual during a hospital stay is not available at the individual level. For reimbursed medications, information about the indication is also included; however, for psychiatric disorders, this is only available from 2008 (2). The medications are classified by the Anatomical Therapeutic Chemical (ATC) classification system.

The Norwegian Patient Registry (NPR) is a health registry containing information about diagnoses given to individuals treated in secondary health care, both in hospitals and out-patient clinics. Diagnoses are registered by the International Classification of Diseases (ICD) codes (at present version 10), and interventions by The NOMESCO Classifications of Surgical, Medical and Radiological Procedures (NCSP, NCMP, NCRP) codes. NPR was established in 1997, but has only had data available for linkage on an individual level from 2008. The Personal Health Data Filing System Act (3, 4) which is further specified in registry-specific regulations, provide the legal basis for the health registries.

The National Educational Database (NUDB), established in 1970, contains information about the level of education of every Norwegian inhabitant from the age of 16 years, from completed lower secondary education to tertiary education including PhD level, and is updated every year (3, 5).

### Appendix S2. Narcolepsy.

ADHD medication may also be used for narcolepsy (*ICD-10* code G47 or ICPC P06). Using the reimbursement codes in NorPD (available from 2008), we found that 674 (0.03%) mothers and 460 (0.02%) fathers to offspring registered born in MBRN, and 791 (0.03%) individuals registered born in MBRN were prescribed stimulants exclusively for narcolepsy in the period 2008-2015. These were excluded from the group of individuals with ADHD. Thus, for patients who were dispensed medication in the period 2004-2008 only, there may be a small number of individuals with narcolepsy left in individuals with ADHD.

### Supporting References:

1. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand.* 2000;79(6):435-9.
2. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol.* 2010;106(2):86-94.
3. Statistics Norway: <https://www.ssb.no/en/>. Oslo. 2019.
4. The Personal Health Data Filing System Act [Internet]. Oslo Ministry of Health and Care Services Available from: <https://lovdatano/dokument/NL/lov/2014-06-20-43> [Accessed February 2019].
5. Steingrimsdottir OA, Naess O, Moe JO, Groholt EK, Thelle DS, Strand BH, et al. Trends in life expectancy by education in Norway 1961-2009. *Eur J Epidemiol.* 2012;27(3):163-71.

**Table S1. Sample characteristics of mothers and fathers<sup>a</sup> with and without ADHD in the study population including offspring born 1967-2011 and followed to 2015. Norway, (N=2 486 088).**

Variables	Mothers and fathers with ADHD +/- or without ADHD-							
	Mother- / Father -		Mother - /Father+		Mother+/Father-		Mother +/Father+	
	No.	%	No.	%	No.	%	No.	%
<b>No. offspring</b>	2 447 559	98.5	16 952	0.7	20 032	0.8	1 545	0.06
<b>Maternal mean age, years (SD)</b>	27.7 (5.3)		25.6 (5.5)		25.6 (5.4)		24.7 (5.2)	
<b>Maternal age at birth</b>	<i>p</i> <.001 <sup>b</sup>		<i>p</i> <.001 <sup>c</sup>		<i>p</i> =.126 <sup>d</sup>		<i>p</i> <.001 <sup>e</sup>	
<20 years	127 452	5.2	2 254	13.3	2 536	12.7	252	16.3
20-24	613 246	25.1	5 683	33.5	6 938	34.6	595	38.5
25-29	838 750	34.3	4 957	29.2	5 783	28.9	394	25.5
30-34	592 188	24.2	2 875	17.0	3 445	17.2	239	15.5
35-39	232 848	9.5	1 013	6.0	1 145	5.7	59	3.8
40+	43 069	1.8	170	1.0	185	0.9	6	0.4
<b>Paternal age at birth</b>	<i>p</i> <.001 <sup>b</sup>		<i>p</i> =.006 <sup>c</sup>		<i>p</i> <.001 <sup>d</sup>		<i>p</i> <.001 <sup>e</sup>	
<20 years	29 167	1.2	870	5.1	722	3.6	88	5.7
20-24	361 163	14.8	4 369	25.8	4 582	22.9	446	28.9
25-29	758 717	31.0	5 295	31.2	6 359	31.7	495	32.0
30-34	707 546	28.9	3 853	22.7	4 754	23.7	291	18.8
35-39	384 394	15.7	1 840	10.9	2 401	12.0	168	10.9
40-44	144 024	5.9	560	3.3	841	4.2	39	2.5
45-49	44 971	1.8	125	0.7	290	1.5	12	0.8
50+	17 577	0.7	40	0.2	83	0.4	6	0.4
<b>Maternal marital status</b>	<i>p</i> <.001 <sup>b</sup>		<i>p</i> <.001 <sup>c</sup>		<i>p</i> <.001 <sup>d</sup>		<i>p</i> <.001 <sup>e</sup>	
Single	184 352 (7.5)	7.5	3 797	22.4	4 562 (22.8)		471	30.5
<b>Couples with at least one offspring with ADHD</b>								
	<i>p</i> <.001 <sup>b</sup>		<i>p</i> <.001 <sup>c</sup>		<i>p</i> <.001 <sup>d</sup>		<i>p</i> <.001 <sup>e</sup>	
<b>Offspring with ADHD, No. (%)</b>	70 191	2.9	3 371	19.9	5 612	28.0	545	35.3
Females	25 460	2.1	1 171	14.3	2 173	23.1	209	28.1
Males	44 731	3.6	2 200	25.1	3 439	32.3	336	42.0

- Excluded children with missing fathers
- Difference between all the three exposure groups relative to the comparison population (Pearson chi-square test and t test for equality of means).
- Difference between both parents having ADHD (mother+/father+) and only the father having ADHD (M-/F+) (Pearson chi-square test and t test for equality of means).
- Difference between both parents having ADHD (M+/F+) and only the mother having ADHD (M+/F-) (Pearson chi-square test and t test for equality of means).
- Difference between only the father having ADHD (M-/F+) and only the mother having ADHD (M+/F-) (Pearson chi-square test and t test for equality of means).

**Table S2. Parent-offspring recurrence of ADHD in offspring (mothers and fathers to offspring born 1999 - 2011, the Medical Birth Registry of Norway).**

	Mothers and fathers with ADHD +/- or without ADHD-			
	Mother- / Father -	Mother - /Father+	Mother+/Father-	Mother+/Father+
<b>Total couple of parents No. (%)</b>	719 636 (97.2)	9 621 (1.3)	10 415 (1.4)	1 101 (0.15)
<b>Crude prevalences No. (%)</b>				
ADHD offspring	19 497 (2.7)	1 455 (15.1)	2 251 (21.6)	290 (26.3)
ADHD daughter	5 297 (1.5)	443 (9.5)	762 (15.5)	106 (19.6)
ADHD son	14 200 (3.9)	1 012 (20.4)	1 489 (27.0)	184 (32.9)
<b>Adjusted prevalences<sup>a</sup> (% ,95% CI)</b>				
ADHD offspring	2.7 (2.7-2.7)	15.9 (15.1-16.7)	21.8 (21.0-22.6)	29.4 (26.5-32.3)
ADHD daughter	1.6 (1.5-1.6)	9.2 (8.7-9.7)	12.4 (11.9-13.0)	17.0 (15.4-18.7)
ADHD son	3.8 (3.7-3.8)	22.1 (21.0-23.1)	29.8 (28.7-30.9)	40.9 (37.0-44.8)
<b>Prevalence difference<sup>a</sup> (% ,95% CI)</b>				
ADHD offspring	0 (ref)	13.1 (12.3-13.8)	18.6 (17.9-19.4)	26.6 (23.8-29.4)
ADHD daughter	0 (ref)	7.6 (7.1-8.1)	10.8 (10.3-11.4)	15.5 (13.8-17.1)
ADHD son	0 (ref)	18.3 (17.2-19.3)	26.0 (25.0-27.1)	37.1 (33.2-41.1)
<b>Relative risk<sup>a</sup> (95% CI)</b>				
ADHD offspring	1.0 (ref)	5.9 (5.6-6.2)	8.0 (7.7-8.4)	10.9 (9.8-12.0)
ADHD daughter	1.0 (ref)	6.7 (6.1-7.4)	10.5 (9.8-11.3)	14.8 (12.6-17.5)
ADHD son	1.0 (ref)	5.5 (5.2-5.8)	7.0 (6.7-7.3)	9.4 (8.4-10.5)

Mother's identification number was used as a cluster variable in all analyses

a. Adjusted for year of birth (5-year groups, from 1967 to 2011, with 1967-1973 as the reference period), CI= confidence interval

**Table S3. Parent-offspring recurrence of ADHD confined to first offspring, born 1967-2011. The Medical Birth Registry of Norway.**

	Mothers and fathers with ADHD +/- or without ADHD-			
	Mother- / Father -	Mother -/Father+	Mother+/Father-	Mother+/Father+
<b>Total couple of parents No. (%)</b>	981 037 (98.2)	8 694 (0.9)	9 070 (0.9)	710 (0.07)
<b>Crude prevalences (%)</b>				
ADHD offspring	29 438 (3.0)	1 710 (19.7)	2 562 (28.3)	256 (36.1)
ADHD daughter	10 486 (2.2)	577 (13.8)	956 (22.7)	92 (27.5)
ADHD son	18 952 (3.8)	1 133 (25.0)	1 606 (33.0)	164 (43.7)
<b>Adjusted prevalences<sup>a</sup> (% ,95% CI)</b>				
ADHD offspring	3.0 (3.0-3.0)	17.6 (16.9-18.3)	24.5 (23.7-25.2)	35.3 (32.2-38.5)
ADHD daughter	2.2 (2.2-2.3)	12.9 (12.3-13.5)	17.8 (17.1-18.4)	25.7 (23.4-27.9)
ADHD son	3.8 (3.7-3.8)	21.9 (21.0-22.8)	30.2 (29.2-31.2)	43.6 (39.8-47.4)
<b>Prevalence difference <sup>a</sup> (% ,95% CI)</b>				
ADHD offspring		14.5 (13.8-15.2)	21.1 (20.4-21.9)	31.8 (28.8-34.9)
ADHD daughter		10.7 (10.1-11.2)	15.6 (14.9-16.2)	23.4 (21.1-25.7)
ADHD son		18.1 (17.2-19.1)	26.4 (25.4-27.4)	39.8 (36.0-43.6)
<b>Relative risk<sup>a</sup> (95% CI)</b>				
ADHD offspring	1.0	5.9 (5.6-6.1)	8.1 (7.9-8.4)	11.3 (10.4-12.4)
ADHD daughter	1.0	6.4 (6.0-6.9)	9.8 (9.2-10.3)	14.2 (12.2-16.6)
ADHD son	1.0	5.5 (5.2-5.8)	7.2 (6.9-7.5)	9.9 (9.0-11.0)

a. Adjusted for year of birth (5-year groups, from 1967 to 1997, with 1967-1973 as the reference period), CI= confidence interval

**Table S4. Parent-offspring recurrence of ADHD confined to first offspring born 1981-2011, mothers and fathers born 1967-1996. The Medical Birth Registry of Norway.**

	<b>Mothers and fathers with ADHD +/- or without ADHD-</b>			
	<b>Mother- / Father -</b>	<b>Mother -/Father+</b>	<b>Mother+/Father-</b>	<b>Mother+/Father+</b>
<b>Total couple of parents No. (%)</b>	256 293 (96.0)	5295 (2.0)	4957 (1.9)	563 (0.2)
<b>Crude prevalences (%)</b>				
ADHD offspring	10 286 (4.0)	1 014 (19.1)	1399 (28.2)	197 (35.0)
ADHD daughter	3 034 (2.4)	330 (13.0)	497 (21.7)	68 (25.6)
ADHD son	7 252 (5.5)	684 (24.7)	902 (33.8)	129 (43.4)
<b>Adjusted prevalences<sup>a</sup> (% ,95% CI)</b>				
ADHD offspring	4.0 (3.9-4.1)	19.1 (18.1-20.2)	28.2 (27.0-29.5)	35.0 (31.1-38.9)
ADHD daughter	2.5 (2.5-2.6)	12.0 (11.3-12.7)	17.5 (16.6-18.4)	21.8 (19.3-24.3)
ADHD son	5.4 (5.3-5.5)	25.7 (24.3-27.1)	37.4 (35.8-39.1)	46.8 (41.6-52.0)
<b>Prevalence difference<sup>a</sup> (% ,95% CI)</b>				
ADHD offspring		19.0 (15.5-22.4)	27.7 (23.8-31.7)	42.2 (27.8-56.6)
ADHD daughter		13.0 (10.5-15.5)	19.0 (16.0-22.0)	29.0 (18.9-39.0)
ADHD son		24.5 (20.1-29.0)	35.9 (30.7-41.0)	54.6 (35.9-73.3)
<b>Relative risk<sup>a</sup> (95% CI)</b>				
ADHD offspring	1.0	4.8 (4.5-5.1)	7.0 (6.7-7.4)	8.7 (7.8-9.8)
ADHD daughter	1.0	5.4 (4.8-6.0)	8.9 (8.2-9.7)	10.5 (8.6-13.0)
ADHD son	1.0	4.5 (4.2-4.8)	6.1 (5.8-6.5)	7.9 (6.9-9.0)

a. Adjusted for year of birth (5-year groups, from 1967 to 1997, with 1967-1973 as the reference period), CI= confidence interval

**Table S5. Parental psychopathology as risk factors of offspring ADHD (mothers and fathers to offspring born 1967-2011, the Medical Birth Registry of Norway).<sup>a,b</sup>**

ADHD offspring by parental	Mother- / Father - <sup>d</sup>	Mother -/Father+ <sup>d</sup>	Mother+/Father- <sup>d</sup>	Mother+/Father+ <sup>d</sup>
<b>BIPOLAR DISORDER</b>				
<b>Total couple of parents No. (%)</b>	2 381 348 (97.3)	26 999 (1.1)	38 435 (1.6)	777 (0.03)
<b>Crude prevalences No. (%)</b>	66 719 (2.8)	1 246 (4.6)	2 173 (5.7)	53 (6.8)
Daughter	24 186 (2.1)	457 (3.4)	800 (4.3)	17 (4.6)
Son	42 528 (3.5)	794 (5.8)	1 373 (7.0)	36 (8.9)
<b>Adjusted prevalences<sup>c</sup> (% ,95% CI)</b>	2.8 (2.8-2.8)	4.3 (4.1-4.6)	5.3 (5.1-5.6)	6.2 (4.4-8.0)
Daughter	2.1 (2.1-2.1)	3.2 (3.0-3.4)	4.0 (3.8-4.1)	4.6 (3.3-5.9)
Son	3.5 (3.5-3.5)	5.4 (5.1-5.7)	6.6 (6.4-6.9)	7.7 (5.5-9.9)
<b>Prevalence difference<sup>c</sup> (% ,95% CI)</b>	0.0 (ref)	1.5 (1.3-1.8)	2.5 (2.3-2.8)	3.4 (1.6-5.1)
Daughter	0.0	1.1 (1.0-1.3)	1.9 (1.7-2.1)	2.5 (1.2-3.8)
Son	0.0	1.9 (1.6-2.2)	3.2 (2.9-3.4)	4.2 (2.0-6.4)
<b>Relative risk<sup>c</sup> (95% CI)</b>	1.0 (ref)	1.5 (1.5-1.6)	1.9 (1.8-2.0)	2.2 (1.7-3.0)
Daughter	1.0	1.5 (1.4-1.7)	1.9 (1.8-2.1)	2.0 (1.3-3.3)
Son	1.0	1.6 (1.5-1.7)	1.9 (1.8-2.0)	2.3 (1.6-3.3)
<b>SCHIZOPHRENIA SPECTRUM DISORDER</b>				
<b>Total couple of parents No. (%)</b>	2 427 811 (99.2)	8 140 (0.3)	11 438 (0.5)	170 (0.01)
<b>Crude prevalences No. (%)</b>	69 213 (2.9)	428 (5.3)	535 (4.7)	15 (8.8)
Daughter	25 086 (2.1)	163 (4.1)	206 (3.8)	5 (6.3)
Son	44 127 (3.6)	265 (6.4)	329 (5.5)	10 (11.0)
<b>Adjusted prevalences<sup>c</sup> (% ,95% CI)</b>	2.9 (2.8-2.9)	4.9 (4.4-5.4)	4.6 (4.2-5.0)	7.7 (3.5-12.0)
Daughter	2.1 (2.1-2.1)	3.6 (3.3-4.0)	3.4 (3.1-3.7)	5.7 (2.6-8.8)
Son	3.5 (3.5-3.6)	6.1 (5.5-6.7)	5.7 (5.2-6.2)	9.5 (4.4-14.7)
<b>Prevalence difference<sup>c</sup> (% ,95% CI)</b>	0.0 (ref)	2.8 (2.3-3.3)	2.4 (2.0-2.8)	5.7 (2.1-9.4)
Daughter	0.0	1.5 (1.2-1.9)	1.3 (1.0-1.6)	3.5 (0.5-6.7)
Son	0.0	2.6 (1.9-3.2)	2.2 (1.7-2.7)	6.0 (0.8-11.2)
<b>Relative risk<sup>c</sup> (95% CI)</b>	1.0 (ref)	1.7 (1.6-1.9)	1.6 (1.5-1.8)	2.7 (1.6-4.7)
Daughter	1.0	1.8 (1.6-2.2)	1.7 (1.5-2.0)	2.7 (1.2-6.5)
Son	1.0	1.7 (1.5-1.9)	1.6 (1.4-1.7)	2.6 (1.4-5.0)
<b>MAJOR DEPRESSIVE DISORDER</b>				
<b>Total couple of parents No. (%)</b>	2 226 724 (91.0)	73 561 (3.0)	136 727 (5.6)	10 547 (0.4)
<b>Crude prevalences No. (%)</b>	59 143 (2.7)	3 323 (4.5)	7 063 (5.2)	662 (6.3)
Daughter	21 631 (2.0)	1 106 (3.1)	2 489 (3.7)	234 (4.6)
Son	37 512 (3.3)	2 217 (5.9)	4 574 (6.5)	428 (7.8)
<b>Adjusted prevalences<sup>c</sup> (% ,95% CI)</b>	2.7 (2.7-2.7)	4.2 (4.0-4.3)	4.8 (4.7-5.0)	5.6 (5.2-6.0)
Daughter	2.0 (2.0-2.0)	3.1 (3.0-3.2)	3.6 (3.5-3.7)	4.1 (3.8-4.5)
Son	3.3 (3.3-3.4)	5.2 (5.0-5.4)	6.0 (5.9-6.2)	6.9 (6.4-7.5)
<b>Prevalence difference<sup>c</sup> (% ,95% CI)</b>	0.0 (ref)	2.1 (2.0-2.3)	2.9 (2.8-3.0)	4.2 (3.7-4.6)
Daughter	0.0	1.1 (1.0-1.2)	1.6 (1.5-1.7)	2.2 (1.8-2.5)
Son	0.0	1.9 (1.7-2.0)	2.7 (2.6-2.9)	3.6 (3.1-4.2)
<b>Relative risk<sup>c</sup> (95% CI)</b>	1.0 (ref)	1.6 (1.5-1.6)	1.8 (1.8-1.9)	2.1 (1.9-2.3)
Daughter	1.0	1.5 (1.4-1.6)	1.8 (1.7-1.9)	2.2 (1.9-2.5)
Son	1.0	1.6 (1.6-1.7)	1.8 (1.8-1.9)	2.0 (1.8-2.2)

a. ADHD in mother and fathers excluded

b. All analyses clustered on mother's ID

c. Adjusted for year of birth (5-year groups, from 1967 to 2011, with 1967-1973 as the reference period), CI= confidence interval

d. Mother/father- means parents without the disorder, and mother/father+ means parents with the disorder

**Table S6. The familial contribution<sup>a</sup> for ADHD in offspring from mothers and fathers with ADHD and other psychiatric disorders, mothers and fathers born 1967-1996. The Medical Birth Registry of Norway.**

	<b>Mother % (SE)</b>	<b>Father % (SE)</b>
<b>ADHD</b>		
ADHD offspring	0.50 (0.003)	0.39 (0.004)
<b>BIOLAR DISORDER<sup>b</sup></b>		
ADHD offspring	0.13 (0.004)	0.09 (0.005)
<b>SCHIZOPHRENIA SPECTRUM DISORDER<sup>b</sup></b>		
ADHD offspring	0.09 (0.007)	0.11 (0.007)
<b>MAJOR DEPRESSIVE DISORDER<sup>b</sup></b>		
ADHD offspring	0.15 (0.003)	0.11 (0.004)

- a. Calculated using tetrachoric correlations
- b. ADHD in parents excluded